Atomoxetine in the Treatment of Binge-Eating Disorder: A Randomized Placebo-Controlled Trial

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Objective: Binge-eating disorder (BED) is associated with obesity. Atomoxetine is a highly selective norepinephrine reuptake inhibitor associated with weight loss. The purpose of this study was to evaluate atomoxetine in the treatment of BED.

Method: In this 10-week, single-center, randomized, double-blind, placebo-controlled, flexible dose (40–120 mg/day) trial, outpatients with DSM-IV-TR BED received atomoxetine or placebo. The primary outcome measure was binge-eating episode frequency. The primary analysis of efficacy was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the effect measure. Patients were enrolled from September 2004 through October 2005.

Results: Compared with placebo (N = 20), atomoxetine (N = 20) was associated with a significantly greater rate of reduction in binge-eating episode frequency, as well as in binge day frequency, weight, body mass index, and scores on the Clinical Global Impressions-Severity of Illness scale, Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating obsession subscale, and Three Factor Eating Questionnaire hunger subscale. The mean (SD) atomoxetine daily dose at endpoint evaluation was 106 (21) mg/day. Four patients (N = 3 receiving atomoxetine, N = 1 receiving placebo) discontinued because of adverse events. The reasons for atomoxetine discontinuation were increased depressive symptoms (N = 1), constipation (N = 1), and nervousness (N = 1).

Conclusion: Atomoxetine was efficacious and fairly well tolerated in the short-term treatment of BED.

Clinical Trials Registration: ClinicalTrials.gov identifier NCT00327834.

(J Clin Psychiatry 2007;68:390–398)

Received May 24, 2006; accepted July 19, 2006. From the Psychopharmacology Research Program, Department of Psychiatry, University of Cincinnati College of Medicine (Drs. McElroy, Guerdjikova, Kotwal, Welge, Nelson, and Keck and Ms. Lake), and Mental Health Service Line and General Clinical Research Center, Cincinnati Veterans Affairs Medical Center (Dr. Keck), Cincinnati, Ohio; and the Department of Psychiatry, Harvard Medical School and McLean Hospital, Belmont, Mass. (Dr. Hudson).

This study was supported in part by a grant from Eli Lilly, Indianapolis, Ind.

Individual financial disclosure can be found at the end of this article.

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Binge-eating disorder (BED) is characterized by recurrent binge-eating episodes without inappropriate compensatory weight loss behaviors.[1,2] Increasing evidence indicates that BED is an important public health problem. Its lifetime prevalence in the United States general population is estimated to be 3%,[3,4] and it is associated with psychopathology, especially anxiety and depressive disorders[4–6]; obesity and other types of medical comorbidity[4,7–9]; impaired quality of life[10]; and disability.[4]

Treatment objectives for BED include reduction of binge eating and associated psychopathology and management of comorbid obesity and related medical conditions.[2,11–16] The National Institute for Clinical Excellence guidelines recommend the use of cognitive-behavioral and interpersonal therapies and selective serotonin reuptake inhibitor (SSRI) antidepressants.[17] All of these treatments, however, have limitations. Both cognitive-behavioral therapy and interpersonal therapy often result in reduced binge eating and associated psychopathology but usually are not associated with clinically significant weight loss.[11,14–16] By contrast, although several SSRIs were associated with statistically significant reductions in binge eating and body weight in short-term, placebo-controlled monotherapy trials,[12,13,18–21] fluoxetine was ineffective for binge eating and weight loss in 2 placebo-controlled studies that compared it with cognitive-behavioral therapy.[14,15] Orlistat with cognitive-behavioral therapy,[22] sibutramine,[23,24] topiramate,[25,26] and zonisamide[27] have been shown in controlled trials to significantly reduce both binge eating and body weight; sibutra-

mine has also been shown to significantly reduce associated depressive symptoms.[23] However, all 4 medications are associated with problematic side effects and relatively high discontinuation rates.[27–30] Novel treatments that reduce binge eating, as well as associated psychopathology and body weight, and that are well tolerated are therefore needed for BED.

Several lines of evidence suggested to us that atomoxetine—a highly specific norepinephrine reuptake inhibitor approved by the U.S. Food and Drug Administration (FDA) for the treatment of attention-deficit/hyperactivity disorder (ADHD)—might be a useful treatment for BED.[31–33] First, the central norepinephrine system is involved in regulating eating behavior,[34] and atomoxetine has been shown to reduce food consumption in several animal models of feeding.[35] Second, atomoxetine was associated with anorexia and weight loss in the registration clinical trials for ADHD in both children and adults.[31–33] It has also been shown to significantly reduce body weight as compared with placebo in a preliminary 12-week study of 30 women with obesity who did not have "major psychiatric disorder or alcohol/substance abuse within the past year."[36(p1139)] Third, a range of antidepressants has been reported to reduce binge eating in BED and the related condition bulimia nervosa, including tricyclics with primarily noradrenergic reuptake inhibiting properties.[12,13,37] Preliminary observations suggest atomoxetine may have antidepressant properties—both in children with ADHD[31,38] and in adults with major depressive disorder.[39,40] Fourth, atomoxetine is generally well tolerated. In the ADHD registration clinical trials, dropout rates for adverse events in both children and adults were low (< 5%), and the most commonly reported side effects, which were gastrointestinal and neurologic, were generally described as mild and transient.[33]

These observations led us to conduct a single-center, randomized, parallel-group, placebo-controlled, flexible-dose study to assess the efficacy and safety of atomoxetine during a 10-week course of treatment in 40 outpatients with BED. We also compared the effects of treatment with atomoxetine and placebo on various metabolic measures, including weight, in this patient group.

METHOD

Patients

Study participants were outpatients at the University of Cincinnati Medical Center who were recruited by radio and newspaper advertisements requesting volunteers for a study of a medication for binge eating. Patients were enrolled into the study if they met the following inclusion criteria: (1) were male or female from 18 to 65 years of age; (2) met DSM-IV-TR criteria for BED[1]; (3) weighed ≥ 85% of the midpoint of ideal body weight for height (according to the Metropolitan Height/Weight tables); and (4) had ≥ 3 binge-eating episodes and ≥ 2 binge days in the week before receiving study medication (confirmed with prospective diaries while the patient received single-blind placebo run in; see outcome measures).

Patients were excluded from participation in the study if they met any of the following criteria: (1) had concurrent anorexia nervosa or bulimia nervosa (by DSM-IV-TR criteria); (2) had a substance use disorder (by DSM-IV-TR criteria) within 6 months of study entry; (3) had a lifetime history of a psychotic disorder, a bipolar disorder, or dementia or other cognitive disorder (by DSM-IV-TR criteria); (4) had a personality disorder that could interfere with diagnostic assessment, treatment, or compliance; (5) displayed clinically significant suicidality or homicidality; (6) had received cognitive-behavioral or interpersonal psychotherapy or behavioral weight management for BED within 3 months of study entry; (7) had a clinically unstable medical illness; (8) had a history of seizures, including childhood febrile seizures; (9) required treatment with any drug that might adversely interact with or obscure the action of the study medication; (10) had clinically significant laboratory or electrocardiogram abnormalities; (11) had received monoamine oxidase inhibitors, tricyclic antidepressants, lithium, antipsychotics, or fluoxetine within 4 weeks prior to randomization; (12) had received other psychoactive medication (other than hypnotics, e.g., zolpidem or zaleplon, as needed for insomnia) within 2 weeks of study medication initiation; (13) had received investigational medications or depot antipsychotics within 3 months prior to randomization; or (14) had previously been treated with atomoxetine. Women were excluded if they were pregnant, lactating, or, if fertile, not practicing a form of medically accepted contraception.

The institutional review board at the University of Cincinnati Medical Center approved the study protocol, and the study was conducted in compliance with the Declaration of Helsinki. All patients signed approved written informed consent forms after the study procedures had been fully explained and before any study procedures were performed. Patients were enrolled from September 2004 through October 2005.

Study Design

This was a 10-week, outpatient, randomized, double-blind, parallel-group, flexible-dose study conducted at the University of Cincinnati Medical Center. The trial consisted of 3 phases: a 1- to 2-week screening period which included a 1-week single-blind placebo run in, during which patients had to display ≥ 3 binge episodes and ≥ 2 binge days in order to be included; a 10-week double-blind treatment period; and a 1-week treatment discontinuation period. Patients were evaluated at least twice during the screening period; after 1, 2, 3, 4, 6, 8, and 10 weeks during the treatment period; and 1 week after study medication discontinuation.

The screening evaluation included an interview for demographic and clinical information and medical, psychiatric, and family histories; the Structured Clinical Interview for DSM-IV-TR (SCID)[41] to establish BED and comorbid Axis I diagnoses; a physical examination; vital signs; height and weight; an electrocardiogram; fasting routine blood chemical and hematological tests; and urinalysis. At this evaluation and each of the following visits, patients were given take-home diaries in which to record any binges and, once study medication was initiated, the number of capsules taken on a daily basis (see outcome measures). At the last visit of the screening period (the baseline assessment), patients were evaluated to see if they continued to meet entry criteria. Patients continuing to meet these criteria were enrolled in the treatment period and randomly assigned in a 1:1 ratio to therapy with atomoxetine or placebo. At each visit following the baseline visit, patients were assessed for number of binges experienced since the last visit, other outcome measures, medication dose, medication compliance ascertained by capsule count, adverse events, use of nonstudy medications, vital signs, and weight.

All study medication was in identical 40-mg capsules supplied in numbered containers and dispensed to patients according to a predetermined randomization schedule. Study medication was begun at 40 mg/day for the first 7 days. At the beginning of the second week of treatment, study medication was increased, as tolerated, to 80 mg/day. At the beginning of the third treatment week, study medication was increased, as tolerated, to 120 mg/day. Study medication could be reduced to a minimum of 40 mg daily because of bothersome side effects at any time during the 10-week treatment period. Patients took all their daily dose of study medication in the morning. However, if patients preferred, they could take 40 mg or 80 mg in the afternoon.

Outcome Measures

The primary outcome measure was the weekly frequency of binge-eating episodes (binge frequency), defined as the mean number of binges per week in the interval between visits (total number of binges in the interval, divided by number of days in the interval, and multiplied by 7). Binges were defined using DSM-IV-TR criteria,[1] and assessed via clinical interview and review of patient take-home diaries, in which patients recorded binges, duration of binges, and food consumed during binges (so that binges could be confirmed by the research assistant and physician investigator working with that particular patient).

Secondary outcome measures were weekly frequency of binge days (days when the patient had 1 or more binges); weight (kg); body mass index (BMI, calculated by dividing body weight in kg by height in m^2); Clinical Global Impressions-Severity of Illness scale (CGI-Severity) and -Improvement scale (CGI-Improvement)[42] scores; Yale-Brown Obsessive Compulsive Scale modified for binge eating (YBOCS-BE)[43] scores; Three Factor Eating Questionnaire (TFEQ)[44] scores; and Hamilton Rating Scale for Depression (HAM-D)[45] total scores.

Weight was obtained with the patient in light clothing without shoes on the same scale zeroed at each measurement. The YBOCS-BE is a modified version of the Yale-Brown Obsessive Compulsive Scale[43] used in previous pharmacotherapy studies of BED[19–21,25–27] (and is available from the authors on request) that measures obsessiveness of binge-eating thoughts and compulsiveness of binge-eating behaviors. The TFEQ (also called the Eating Inventory) is a self-report questionnaire that measures 3 dimensions of eating behavior thought to be dysregulated in obesity: cognitive restraint in eating (cognitive restraint); disinhibition of control over eating (disinhibition); and perceived hunger (hunger).[44] As done in most previous BED pharmacotherapy studies, response categories were tabulated based on percentage decrease in frequency of binges from baseline (the week before treatment initiation) to endpoint (the final week of treatment). These categories were defined as follows: remission = cessation of binges; marked = 75%–99% decrease; moderate = 50%–74% decrease; and none = less than 50% decrease. In addition, time to recovery was assessed, defined as the first 4 consecutive weeks during which the patient had no binge-eating episodes.

The following safety measures were assessed: adverse events, clinical laboratory data, physical examination findings, and vital signs. Reportable adverse events were new symptoms or illnesses that occurred during the treatment phase and those that increased in severity compared with baseline.

Statistical Methods

The baseline characteristics of each group were compared by using Fisher exact test for categorical variables and independent-samples t tests for continuous variables.

The primary efficacy analysis was a longitudinal analysis comparing the rate of change of binge frequency during the treatment period between groups. The same analysis was applied to binge day frequency, weight, BMI, and scores on the CGI-Severity, YBOCS-BE, TFEQ, and HAM-D scales. The difference in rate of change was estimated by random regression methods, as described in Fitzmaurice et al.[46] and Gibbons et al.,[47] and as used in several pharmacotherapy studies of BED.[18–21,23–27] We used a model for the mean of the outcome variable that included terms for treatment, time, and treatment-by-time interaction. Time was modeled as a continuous variable, expressed as the square root of days since randomization (baseline). For the analyses of binge frequency and binge day frequency, we used the logarithmic transformations log ([binges/wk] + 1) and log ([binge

Table 1. Baseline Characteristics of Patients With Binge-Eating Disorder Randomly Assigned to 10 Weeks of Double-Blind Treatment With Atomoxetine or Placebo

	Atomoxetine (N = 20)		Placebo (N = 20)	
Characteristic	Mean	SD	Mean	SD
Age, y	43.1	10.2	39.2	7.7
Binge frequency (per week)	4.2	1.4	4.9	2.5
Binge day frequency (per week)	3.8	1.1	3.9	1.5
Assessment scores				
Clinical Global Impressions-Severity of Illness scale	4.2	0.4	4.4	0.6
Hamilton Rating Scale for Depression	2.0	2.4	3.3	3.6
Yale-Brown Obsessive Compulsive Scale (modified for binge eating)	17.4	4.8	17.9	3.1
Obsessions	9.0	3.1	8.6	2.0
Compulsions	8.4	2.1	9.3	1.6
Weight, kg	106.9	20.2	116.6	30.1
Body mass index, kg/m^2	37.3	6.7	41.4	8.5
Female, N	16	80.0	17	85.0
Caucasian, N	17	85.0	17	85.0
Depressive disorder diagnosis, N[a]				
Current	1	5.0	5	25.0
Lifetime	9	45.0	10	50.0

[a]Includes 16 patients with major depressive disorder, 2 with dysthymia, and 1 with depressive disorder not otherwise specified.

days/wk + 1]), respectively, to normalize the data and stabilize the variance. To simultaneously account for individual differences in initial level of the outcome, rate of change over time, and serial autocorrelation (i.e., the tendency for correlation among observations to decrease as a function of the amount of time between them), we used the SAS procedure MIXED version 9.1 (SAS Institute, Inc., Cary, N.C.), with random intercept and slope terms, and a first-order antedependence structure for the residual correlation matrix. The longitudinal analyses were intent-to-treat, using all available observations from all time points from all patients who completed a baseline evaluation.

Several secondary analyses were performed. Using the last observation carried forward (LOCF), baseline to endpoint change scores were computed for each measure (on the logarithmic scale for the bingeing measures), and independent-samples t tests were used to compare these changes between the treatment groups. The Cochrane-Armitage exact trend test for 2-by-k ordered tables in SAS (PROC FREQ) version 9.1 was used to analyze categorical response to treatment (as defined in the previous paragraph) for the intent-to-treat and completer groups.

For laboratory measures, including weight, the mean difference between endpoint and baseline measures was computed for each treatment group and then compared using the t test. The correlation between percentage change in binge frequency and change in weight was calculated using rank-transformed data (Spearman rank correlation). Time to recovery (defined as the first 4 consecutive binge-free weeks after baseline) was analyzed with a Cox proportional-hazards model for the intent-to-treat population.

All statistical tests and confidence intervals were 2-sided, $\alpha = .05$.

RESULTS

Overall, 76 patients were screened, 36 were not enrolled because they chose not to participate (N = 6) or did not meet entry criteria (N = 30), and 40 patients who met entry criteria were randomly assigned to atomoxetine (N = 20) or placebo (N = 20). Thirty-three patients (82.5%) were women, 34 (85%) were white, 5 (12.5%) were African American, and 1 (2.5%) was Asian. Depressive disorders were the most common co-occurring psychiatric disorders, occurring in 19 patients (47.5%) as lifetime diagnoses, and currently in 6 patients (15%). There were no significant differences between the treatment groups in demographic or clinical variables at baseline (Table 1).

Thirty-nine patients (20 receiving atomoxetine and 19 receiving placebo) had at least 1 postrandomization efficacy measure. Six patients (30%) in the atomoxetine group and 9 patients (45%) in the placebo group did not complete all 10 weeks of treatment (Fisher exact p = .51). Four patients withdrew from the study because of adverse events (atomoxetine: N = 3; placebo: N = 1); 1 withdrew because of lack of efficacy (placebo); and 10 withdrew because of nonadherence to the protocol (atomoxetine: N = 3; placebo: N = 7). The remaining 25 patients (62.5%) completed the 10 weeks of treatment (N = 14 receiving atomoxetine and N = 11 receiving placebo).

The mean frequency of binges decreased over the study period in both treatment groups, but more so in the atomoxetine group (Figure 1). Mean body weight decreased over the study period in the atomoxetine group but not in the placebo group (Figure 2).

The primary efficacy analysis using random regression showed that patients receiving atomoxetine had a significantly greater rate of reduction in binge episodes per week than patients receiving placebo (Table 2). Atomoxetine was also associated with a significantly greater rate of improvement than placebo for the following variables: binge days per week, body weight, BMI, and scores on the CGI-Severity, YBOCS-BE total and obsession subscale, and TFEQ hunger subscales (Table 2). However, there was no difference in the rate of change in reduction in YBOCS-BE compulsion subscale scores or TFEQ scores for cognitive restraint or disinhibition between the treatment groups. There was also no difference in the rate of change in HAM-D scores between the treatment groups (Table 2).

In the secondary analysis of baseline-to-endpoint change scores using LOCF, atomoxetine was associated with significant decreases in binges per week, binge days per week, weight, BMI, and scores on the CGI-Severity and the YBOCS-BE total and obsession scales compared

Figure 1. Mean Binge Frequency Over 10 Weeks of Treatment in Patients With Binge-Eating Disorder Randomly Assigned to Atomoxetine or Placebo

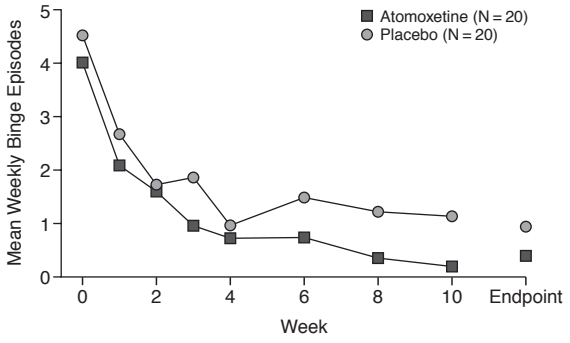

Figure 2. Mean Weight Change in Patients With Binge-Eating Disorder Randomly Assigned to 10 Weeks of Double-Blind Treatment With Atomoxetine or Placebo

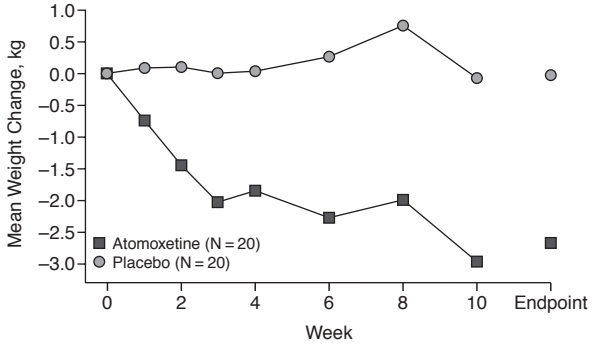

Table 2. Mean Model-Based Differences Between Atomoxetine and Placebo Groups in Change From Baseline to Week 10 for Patients With Binge-Eating Disorder (N = 40) Randomly Assigned to 10 Weeks of Double-Blind Treatment With Atomoxetine or Placebo

	Longitudinal Analysis[a]				Endpoint Analysis[b]			
Outcome Measure	Estimate	95% CI	χ^2 (df = 1)	p*	Estimate	95% CI	t (df = 55)	p*
Binges/week[c]	–0.41	(–0.61 to –0.09)	5.72	.018	–0.16	(–0.29 to –0.01)	2.20	.034
Binge days/week[d]	–0.45	(–0.63 to –0.18)	8.75	.003	–0.17	(–0.30 to –0.03)	2.37	.023
Clinical Global Impressions-Severity of Illness Scale	–1.12	(–2.01 to –0.22)	6.03	.015	–1.20	(–1.90 to –0.50)	3.48	.013
Hamilton Depression Rating Scale	0.58	(–1.33 to 2.49)	0.36	.551	–0.15	(–2.13 to 1.83)	0.15	.879
Yale-Brown Obsessive Compulsive Scale (modified for binge eating)	–4.77	(–9.25 to –0.28)	4.40	.037	–5.30	(–9.01 to –1.59)	2.89	.006
Obsessions	–3.04	(–5.41 to –0.66)	6.36	.012	–3.50	(–5.73 to –1.27)	3.18	.003
Compulsions	–1.82	(–4.26 to 0.63)	2.15	.143	–1.80	(–3.71 to 0.11)	1.91	.067
Three Factor Eating Questionnaire[e]	–3.54	(–8.32 to 1.24)	2.15	.142	–3.80	(–9.44 to 1.84)	1.44	.164
Cognitive restraint	2.08	(–1.38 to 5.54)	1.42	.234	2.01	(–2.47 to 6.49)	0.93	.364
Disinhibition	–1.96	(–4.91 to 0.99)	1.73	.189	–1.94	(–5.47 to 1.60)	1.10	.287
Hunger	–3.56	(–7.15 to 0.02)	3.88	.049	–3.87	(–8.56 to 0.82)	1.70	.104
Weight, kg	–3.09	(–5.46 to –0.72)	6.61	.010	–2.69	(–4.88 to 0.49)	2.48	.018
Body mass index, kg/m^2	–1.03	(–1.86 to –0.20)	5.93	.016	–0.89	(–1.66 to –0.12)	2.34	.025

[a]Estimate is for mean (week 10 minus baseline) for atomoxetine minus mean (week 10 minus baseline) for placebo. Test statistic is the treatment-by-time interaction term, which represents the difference in rate of change between the atomoxetine and placebo groups, with time modeled as square root of days since randomization. The estimate and its CI were obtained by multiplying the treatment-by-time interaction and its CI by 112 (112 days in 16 weeks) and squaring.
[b]Estimate is for mean (week 10 minus baseline) for atomoxetine minus mean (week 10 minus baseline) for placebo. The estimate is the test statistic, which is the mean difference in change scores (endpoint minus baseline) between the atomoxetine and placebo groups.
[c]Log transformation (log [binges/week] + 1) was used for analysis; values in table are expressed in the original scale.
[d]Log transformation (log [binge days/week] + 1) was used for analysis; values in table are expressed in the original scale.
[e]Measured at weeks 0, 4, 8, and 10 only.
*Significant at $p \leq .05$.

with placebo (Table 2). A marginally nonsignificant change was obtained for the YBOCS-BE compulsion subscale scores. There were no significant differences between groups in the changes in scores on the TFEQ or the HAM-D scales.

Regarding global responses, the mean final CGI-Improvement at endpoint was rated much or very much improved in 16 atomoxetine-treated patients (80%) as compared with 8 placebo-treated patients (42%). In the categorical response analyses, there were significantly higher levels of response for atomoxetine-treated patients in both the intent-to-treat and completer groups (Table 3). In the intent-to-treat population, remission of binge episodes was attained by 70% of atomoxetine-treated patients at endpoint compared with 32% of placebo-treated patients (Fisher exact p = .026). Atomoxetine was not associated with shortened time to recovery of binge eating in the intent-to-treat group (hazard ratio for recovery = 0.62, $\chi^2 = 0.44$, p = .508).

Patients receiving atomoxetine experienced a mean (SD) weight loss of 2.7 (3.7) kg from baseline to endpoint, whereas those receiving placebo experienced a mean (SD) weight loss of 0.0 (3.2) kg. Among patients who completed the 10 weeks of treatment, the corre-

Table 3. Response to Treatment Among Patients With Binge-Eating Disorder Randomly Assigned to 10 Weeks of Double-Blind Treatment With Atomoxetine or Placebo

	Intent-to-Treat Group[b]		Patients Who Completed 10 Weeks of Treatment[c]	
Response[a]	Placebo (N = 19), N (%)	Atomoxetine (N = 20), N (%)	Placebo (N = 11), N (%)	Atomoxetine (N = 14), N (%)
None	5 (26)	4 (20)	2 (18)	1 (7)
Moderate	8 (42)	0 (0)	5 (45)	0 (0)
Marked	0 (0)	2 (10)	0 (0)	2 (14)
Remission	6 (32)	14 (70)	4 (36)	11 (79)

[a]Categories defined by the percentage decrease in binge frequency from baseline: remission = cessation of binges; marked = 75%–99% reduction; moderate = 50%–74% reduction; none = less than a 50% reduction.
[b]Patients had at least 1 postrandomization efficacy measure; significant difference between groups (p = .025, exact Cochrane-Armitage trend test).
[c]Significant difference between groups (p = .019 exact Cochrane-Armitage trend test).

sponding weight losses were 3.9 (3.3) kg and 0.2 (4.3) kg. Weight loss since baseline was significantly correlated with percentage reduction in binge frequency at week 10 in the overall sample (Spearman $\rho = -0.49$, $p = .012$). Among patients receiving atomoxetine, this correlation was not significant (Spearman $\rho = -0.15$, $p = .52$), but this result can be attributed in part to the fact that so many of these patients (14 of 20) had no bingeing by week 10, so that only 7 unique ranked values existed in the sample.

There were no significant differences between patients receiving atomoxetine and those given placebo in mean change from baseline to final visit for the fasting measurements of insulin (–2.7 and –1.8 μu/mL; p = .67), glucose (7.5 and –1.6 mg/dL; p = .30), triglycerides (5.5 and –29.0 mg/dL; p = .21), LDL cholesterol (–0.2 and 5.4 mg/dL; p = .61), and total cholesterol (–0.7 and –2.4 mg/dL; p = .88).

The mean (SD) daily dose of atomoxetine at endpoint evaluation for all 20 patients was 106 (21) mg. The mean (SD) daily dose for the 14 patients who completed the 10-week trial was 109 (19) mg.

Adverse events occurring in at least 2 patients receiving atomoxetine are listed in Table 4. Adverse events appeared to be more common overall with atomoxetine than with placebo, and there were statistically significant differences between treatment groups in the incidence of dry mouth. More patients discontinued atomoxetine (N = 3; 15.0%) for adverse events than placebo (N = 1; 5.0%), but this difference in incidence was not statistically significant (Fisher exact p = .60). Adverse events causing discontinuation among atomoxetine-treated patients were increased depressive symptoms (N = 1), constipation (N = 1), and nervousness (N = 1). The adverse event causing discontinuation in the placebo-treated patient was increased blood pressure. No patient experienced a serious adverse event during the study.

Table 4. Adverse Events Reported by ≥ 2 Patients With Binge-Eating Disorder Receiving Treatment With Atomoxetine or Placebo

	Atomoxetine (N = 20)		Placebo (N = 20)	
Adverse Event	N	%	N	%
Dry mouth[a]	11	55	4	20
Nausea	8	40	2	10
Nervousness	7	35	3	15
Insomnia	7	35	3	15
Headache	6	30	4	20
Constipation	4	20	2	10
Sweating	4	20	0	0
Dizziness	3	15	0	0
Hypertension	2	10	1	5
Dyspepsia	2	10	1	5
Somnolence	2	10	2	10
Diarrhea	2	10	2	10
Rhinitis	2	10	2	10
Hot flash	2	10	1	5
Depression	2	10	0	0
Abdominal pain	0	0	2	10
Urinary hesitancy	2	10	0	0
Eructation	2	10	0	0

[a]Dry mouth (p = .048) occurred more frequently in the atomoxetine group than the placebo group.

There were no changes in physical examination findings, vital signs, or clinical laboratory values suggestive of drug-related toxicity. There was no evidence of withdrawal symptoms in the 6 patients who discontinued atomoxetine prematurely or in the 14 patients who discontinued atomoxetine per protocol.

DISCUSSION

In the primary longitudinal analysis of this randomized, double-blind trial in patients with BED, atomoxetine was significantly superior to placebo in rate of reduction of binge frequency, binge day frequency, body weight, BMI, obsessive-compulsive features of binge-eating symptoms, hunger, and overall severity of illness. A secondary analysis, change from baseline to endpoint using LOCF, yielded similar positive findings, with atomoxetine being associated with significant decreases in binge frequency, binge day frequency, body weight, BMI, obsessive-compulsive features of binge-eating symptoms, and overall severity of illness compared with placebo. Atomoxetine was also associated with a significantly higher level of categorical response in both the endpoint and completer analyses, but not with a shortened time to recovery of binge eating, although the relatively modest sample size and length of follow-up may explain this result. The mean weight loss in the intent-to-treat group receiving atomoxetine was 2.7 kg, as compared with 0.0 kg in the group receiving placebo. There was no significant change in HAM-D scores, but mean HAM-D scores were low at baseline. Taken together, these findings provide preliminary evidence for the efficacy of atomoxetine in BED.

The reduction in binge frequency and overall improvement observed with atomoxetine in this study appear comparable to results reported in studies of cognitive-behavioral therapy,[11,14–16] interpersonal therapy,[11] SSRIs,[12,13,18–21] sibutramine,[23,24] topiramate,[25,26] zonisamide,[27] and orlistat plus cognitive-behavioral therapy[22] in patients with BED. The weight loss appears comparable to that seen for sibutramine,[23,24] topiramate,[25,26] zonisamide,[27] and orlistat with[22] or without[48] cognitive-behavioral therapy. However, the high premature discontinuation rate also seems comparable to that seen for the latter treatments[22,23,25–27,47] and for SSRIs.[18–21] Appropriately designed controlled comparison trials are required to accurately determine atomoxetine's efficacy, tolerability, and safety relative to other treatments of BED, as well as where it will fit into the growing therapeutic armamentarium for this condition.

The potential mechanism of action of atomoxetine in BED is unknown. Since the central norepinephrine system is involved in the regulation of feeding behavior[34] and atomoxetine is a highly selective norepinephrine reuptake inhibitor,[31–33] one possible mechanism by which atomoxetine might reduce binge eating is decreasing appetite or enhancing satiety through its effects on this system. Decreased binge eating might lead to reduced energy intake and, secondarily, to weight loss. Alternatively, a second possible mechanism is that atomoxetine might reduce binge eating via its gastrointestinal side effects. A third possible mechanism is that atomoxetine may secondarily decrease binge eating through direct weight loss effects. For example, compounds with noradrenergic properties have been hypothesized to induce weight loss in part by increasing locomotor activity or enhancing thermogenesis.[33,49]

Several limitations of this study should be considered. First is that the attrition rate was high, with 37.5% of patients withdrawing before study completion. This feature renders the results heavily dependent on assumptions regarding missing data.[46,47,50] While the longitudinal analysis, unlike the endpoint analysis, allows that the missingness can depend on observations obtained before withdrawal (e.g., a patient who is failing to improve may be more likely to withdraw), it is nevertheless vulnerable to missingness that depends on factors that are not measured prior to withdrawal (technically, missing not at random or non-ignorable missingness). Of note, although the 37.5% attrition rate in our study is substantially higher than the overall attrition rates of < 5% seen in the initial clinical trials of atomoxetine in ADHD, it is comparable to the 30% attrition rate in the Gadde et al. 12-week study of atomoxetine in obese women.[36] The 2 most common reasons for dropout while taking atomoxetine in the present study were protocol nonadherence (15%) and adverse events (15%). In the Gadde et al. study, 1 patient (3%) dropped out for an adverse event (rapid heartbeat with atomoxetine), and the other reasons (N = 8; 26.7%) could be attributed to difficulty with protocol adherence; they included time constraints (N = 3 atomoxetine, N = 1 placebo), lost to follow-up (N = 1 atomoxetine, N = 1 placebo), relocation (N = 1 atomoxetine), and withdrawal of consent (N = 1 placebo). It is thus noteworthy that attrition is a significant problem in clinical trial research in both obesity[51] and bulimia nervosa,[52,53] 2 conditions related to BED.[2]

Research into why attrition rates are high in pharmacotherapy studies of BED are needed; such studies could possibly focus on impulsivity, treatment expectations, and logistics factors that have been associated with attrition in treatment studies of obesity[54,55] and bulimia nervosa.[52,56] Such research might generate information that will lead to increased completion rates in clinical trials in persons with eating disorders or obesity.

A second limitation is that the accuracy of the self-report methods used to obtain binge-eating data is uncertain.[57,58] However, patient diaries were used to enhance patient recall of binges, and randomization and double-blinding should have equalized any patient or investigator bias in the recording or rating of overeating episodes as binges. A third limitation is that because the study group was small and primarily female and white, and the duration of treatment was short (10 weeks), the results may not generalize to larger groups of persons with BED, to males or African Americans with BED, or to longer treatment periods. A fourth limitation is that because persons with psychotic disorders, bipolar disorders, substance use disorders, severe personality disorders, and unstable medical disorders were excluded, the results may not generalize to BED when it co-occurs with these conditions.

In summary, in a 10-week trial in outpatients with BED, atomoxetine was found to be superior to placebo in reducing binge frequency, weight, and severity of illness. It was also associated with fairly good tolerability but a relatively high treatment discontinuation rate. Controlled trials of atomoxetine in larger groups of patients with BED appear warranted.

Drug names: atomoxetine (Strattera), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), orlistat (Xenical), sibutramine (Meridia), topiramate (Topamax), zaleplon (Sonata), zolpidem (Ambien), zonisamide (Zonegran and others).

Financial disclosure: Dr. McElroy is a consultant to or member of the scientific advisory boards of Abbott, Eli Lilly, GlaxoSmithKline, Janssen, Ortho-McNeil, and Wyeth-Ayerst; and is a principal or co-investigator on research studies sponsored by AstraZeneca, Bristol-Myers Squibb, Esai, Eli Lilly, Forest, National Institutes of Mental Health (NIMH), Ortho-McNeil, Pfizer, Sanofi-Synthelabo, and Somaxon. Dr. Kotwal is a speaker for Bristol-Myers Squibb. Dr. Nelson has received grant/research support from Eli Lilly and AstraZeneca. Dr. Keck is a consultant to or member of the scientific advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Memory Pharmaceuticals, Neurocrine Biosciences, Pfizer, and Shire; and is a principal or co-investigator on

research studies sponsored by Abbott, American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Janssen, Memory Pharmaceuticals, Merck, NIMH, National Institute of Drug Abuse, Organon, Ortho-McNeil, Pfizer, Stanley Medical Research Institute, and UCB Pharma. Dr. Hudson is a consultant to and has received grant/research support from Eli Lilly and Ortho-McNeil, and serves on the speakers or advisory board for Eli Lilly. Drs. Guerdjikova and Welge and Ms. Lake report no other significant commercial relationships relevant to the study.

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